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# Use of Probiotic in Preventing Antibiotic-Associated Diarrhea

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# Use of Probiotic in Preventing Antibiotic-Associated Diarrhea Benchmark Study

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## Executive Summary

Antibiotic-associated diarrhea (AAD) including *Clostridium difficile* associated diarrhea (CDAD) has been a challenging topic for the healthcare industry. AAD is caused by the disruption of normal microbial balance along with the gastrointestinal (GI) tract due to the use of an antibiotic. AAD not only increases healthcare cost burden but also increases morbidity and mortality among vulnerable populations such as the elderly. Antibiotic use is very common among the elderly and it is the responsibility of healthcare providers to take appropriate measures in preventing complications associated with antibiotic use among these populations. Therefore, exploring measures that are cost-effective to prevent the complication of antibiotic use in vulnerable populations is important for any provider. The PICOT question for this study is as follows: In patients 65 years and older (P), how does the use of probiotic (I) compared to non-use of probiotic therapy (C) affect the risk of antibiotic-associated diarrhea (O) during or within 12 weeks of antibiotic therapy (T)?

Easily available, tolerable, and cost-effective probiotics can be life-saving measures for many elderly populations if it is effective in preventing AAD and CDAD. Probiotics are generally well documented for the benefits they provide on gastrointestinal and immune health. It is also considered safe to consume for most age groups. Elderly patients are admitted or readmitted frequently to the hospital with infections such as urinary tract infection (UTI), sepsis, and pneumonia every day and they encounter many complications due to antibiotic treatment and hospitalization itself. Hospitalization can be more devastating to elderly patients as they are more prone to complications related to hospitalization such as delirium, debility, decrease mobility, skin breakdown, and falls. Based on the literate review of twelve articles that include

mostly systemic reviews and randomized control trials (RCTs), there are some promising results in preventing AAD and CDAD with probiotic use.

This project seeks to introduce and implement the protocol of prescribing probiotic *Culturelle* along with the antibiotic in the medical-surgical geriatric unit of the hospital. The main purpose of this study is to evaluate the effect of probiotics in preventing AAD and CDAD when concurrently used with antibiotics among the elderly.

## Rationale for the Project

The elderly who are more susceptible to disease because of diminished physiological reserve and immune response are more likely to receive long-term antibiotics (Mallina et al., 2018). The practice of prescribing antibiotics has also been drastically changed over the last decade due to the emergence of many drug resistance infections including Clostridium difficile infection (CDI). When it comes to elderly patients, it is important to take preventive measures for AAD and CDAD. The cost burden and mortality related to ADD including CDAD among the elderly is high in today's healthcare industry. According to Mallina et al., "90% of all CDAD attributed deaths occur in person over the age of 65" (2018, p. 85). According to Allen et al. (2012), approximately 5%-39% of people suffer from AAD during or even up to 12 weeks following antibiotic therapy and about 15%-35% are associated with Clostridium difficile. Probiotics have been well documented as an effective measure to prevent or improve AAD among the pediatric and adult population. Probiotic has a minimal adverse effect and can be cost-effective measures if proven to have a role in preventing or even improving ADD symptoms among the elderly population. Probiotics have been taken in the form of fermented foods for many centuries and are generally considered safe to use among the elderly unless the presence of serious health conditions such as a compromised immune system (Smith, 2016). So, it would be

beneficial to know the role of probiotics when receiving antibiotics among elderly patients. This evidence can be applied into practice to provide the best possible care for the elderly population to increase their quality of life and experience.

## Literature Review

A systematic review of 26 RCTs by Lau and Chamberlain (2016) suggested that CDAD was significantly reduced by the use of probiotic $RR = 0.395$ [95% CI 0.294-0.531], $p < 0.001$). Lau and Chamberlain (2016) found very few trials on elderly patients suggesting a need for more randomized placebo-controlled trials for elderly patients who are at the highest risk of developing AAD and CDAD. Similarly, a systematic review conducted by Xie, Li, Wang, Li, and Chen (2015) showed only one trial where *Bacillus licheniformis* was effective against AAD in older patients; all other probiotics selected in trials did not show a significant reduction in the risk of AAD and CDAD among older adults. Xie et al. (2015) expressed difficulty concluding as there was not adequate data published on the elderly population suggesting a need for a more robust, large sample, and multi-center double-blind RCTs. Wright, Wright, and Murray (2015), who conducted a multi-center randomized controlled pilot study of 87 elderly patients age greater than 65 years, compared an active *Yakult* (contains commercially available probiotic strain, *Lactobacillus casei*) with placebo. The result showed no significant difference in the incidence of diarrhea between *Yakult* and placebo groups with Fisher's exact test, $p = 0.729$ (Wright, Wright, & Murray, 2015).

Pattani, Palda, Hwang, and Shah (2013) conducted a systematic review and meta-analysis of 16 RCTs. Their analysis showed that there was a significant reduction in the risks of AAD and *Clostridium difficile* infection (CDI) among the patients who received probiotics compared to placebo or no treatment. Meta-analysis showed benefits of probiotics on outcomes regardless

of the type of probiotics, quality of a study, and duration of follow-up, but only good quality studies showed significant results for both AAD and CDI (Pattani, Palda, Hwang, & Shah, 2013). Pattani and colleagues (2013) concluded that probiotics can be recommended to prevent both AAD and CDAD for inpatients adults who require antibiotic therapy. Avadhani and Miley (2011) conducted a meta-analysis of eight RCTs that included hospitalized adult patients of age 18 to 80 years who received antibiotics with the exclusion of pre-existing gastrointestinal disease (GI) and immunocompromised patients. Avadhani and Miley (2011) found *RR* of 0.56 at 95% CI (0.44-0.71) $p < 0.001$ for AAD and *RR* of 0.29 at 95% CI (0.18-0.46), $p < 0.001$ for CDAD. The study showed a protective effect of probiotics with significant relative risk reduction (RRR) for both AAD (44%) and CDAD (71%) in probiotic groups compared to placebo or no treatment group when probiotics were used concurrently with antibiotics (Avadhani & Miley, 2011). Safdar, Barigala, Said, and McKinley (2008) indicated that *Lactobacillus acidophilus* based probiotic *Florajen*® was well tolerated without any major adverse effect among elderly with multiple comorbidities. Safdar and associates (2008) found 37% AAD in placebo group and 17% in Florajen® group (*RR* =1.63 ([95% CI 0.73-3.65], $p = 0.15$).

A randomized, double-blind, placebo-controlled trial conducted by Ehrhardt et al. (2016) showed a hazard ratio of 1.02 (95% CI, .55–1.90; $p = .94$) in *Saccharomyces boulardii* group when compared to the placebo group. Ehrhardt et al. (2016) claimed that this was one of the largest RCTs that studied a total of 477 patients; however, 185 patients who did not complete the documentation for daily stools throughout the observation were also included. The trial was stopped due to recruitment issues and low estimated power (Ehrhardt et al., 2016). Mallina et al. (2018) conducted a retrospective cohort study using probiotic ACTIMEL containing

*Lactobacillus casei, Lactobacillus bulgaricus*, and *Streptococcus thermophiles* found no significant decrease in the incidence of CDAD in patients receiving probiotics (*OR* = 0.9 ([95% CI 0.27-2.91], *p* = 0.8). However, Mallina and colleagues (2018) mentioned that reported CDAD rates may be influenced by the lack of antibiotic resistance test of the strains presented in ACTIMEL.

A pilot RCT conducted by Barker et al. (2017) found a significant improvement in diarrhea symptoms with probiotic adjunct therapy along with antibiotic therapy in patients with initial mild to moderate CDAD. The purpose of the study was to determine the feasibility and health outcome of probiotic use. A total of 31 patients were randomized into a daily placebo or a single multi-strain oral probiotic capsule for four weeks. The study showed that the median duration of diarrhea for the placebo group was one day longer in comparison to the probiotic group (*p*=0.039). Similarly, the outcome of total diarrhea days for the placebo group was 12 days and for the probiotic group was 3.5 days respectively. All outcome studies including diarrhea rate (0.1 for probiotic and 0.3 for placebo) were improved in the probiotic group (Barker et al., 2017).

A systematic review and meta-analysis of a total of 82 RCTs by Hempel et al. (2012) concluded that probiotic use was associated with a decrease in AAD incidents (RR = 0.58 [95% CI 0.50-0.68], $p < 0.001$). This systematic review study broadly evaluated the available evidence on the role of probiotics in preventing or treating AAD. Study analysis included all age groups including children, adult, and elderly patients. However, there were only 3 RCTs exclusively in elder patients. Article by Cai et al. (2018) explored the efficacy and tolerability of various probiotics used in preventing or treating AAD with the purpose of ranking and determining the optimal regimen. The authors conducted a meta-analysis of 51 RCTs that used different kinds of

probiotics therapy to prevent AAD and it was concluded that *Lactobacillus rhamnosus GG* (LGG) was ranked the highest in term of both tolerances (OR=0.44, 95% CI 0.23-0.84) and effectiveness (OR=0.28 95% CI 0.17-0.47) in preventing AAD (Cai et al., 2018). A pragmatic participatory evaluation (PPE) design-retrospective cohort study by van Wietmarschen, Busch, van Oostveen, Pot, and Jong (2020) found antibiotic with probiotic use group had significantly lower AAD in comparison to no probiotics use (20% vs 36%, p = 0.022). The authors had also mentioned in their review of literature that the previous studies that showed no difference between multispecies probiotics in comparison to placebo in preventing AAD in older (greater or equal to 65 years) had probiotics administered up to 7 days after start of antibiotics rather than at the start of antibiotic therapy (van Wietmarschen et al., 2020). Therefore, the outcome might be different if probiotics are given along with antibiotics from day one and continue after completion of antibiotics up to 12 weeks to see true results of the effectiveness of probiotics.

## Project Stakeholders

Primary stakeholders for this project include patients or families and providers. Other stakeholders for this change project may include the senior leadership team, the infection control team, nurses who provide direct patient care to these patients, nursing assistants, the manager in this particular unit, supervisor, charge nurses, geriatric physician or nurse practitioner, and clinical educator. The evidence-based practice (EBP) committee of the hospital will be also an important stakeholder of this project.

## Implementation and Evaluation

This project will be carried out in the medical-surgical geriatric unit of the hospital. The patients admitted in this unit are in fairly stable condition who does not need a close monitor or cardiac monitor. Severely immunocompromised patients will not be included in this protocol

unless specifically ordered by a physician. Also, these patients should be able to take pills via the oral or PEG route.

Another important aspect of this project is to educate patients/families and nurses regarding assessing stool consistency using the Bristol Stool Scale. Nurses need education on AAD/CDAD and the importance of accurate assessment of stools as well as accurate and proper documentation of stools in an electronic charting system that helps the nurse manager to generate accurate data on the AAD and CDAD rate. The computer charting system already has a detailed description along with the picture of the Bristol Stool Scale for nurses to pick options from type 1 to type 7 stool. That ensures accurate charting on the types of stool. There will be a copy of the Bristol Stool Scale chart available for patients or can be placed on the wall of the patient's bathroom. Nurse Manager to ensure that all nurses are updated on online mandatory courses regarding AAD/CDAD and use of the Bristol stool scale. Probiotic *Culturelle* will be prescribed daily for all the patients who need antibiotics. There will be a copy of the excel spreadsheet that is provided to the patient or caregiver along with a Bristol Stool Scale to record the number of stools and consistency every day until 12 weeks. The primary nurse will be responsible for educating the patient/family regarding the excel sheet and the Bristol stool scale recording. Discharge follow-up will be made every week by the nurse clinician until 12 weeks to ensure medication and stool record compliance and will be recorded/updated in an electronic health record by the clinician.

The final step of this project will be analyzing the overall data and preparing the final results in a numeric form such as a frequency and percentage or rate as well as a visual form such as a chart. Evaluation of this project includes comparing the AAD rate, CDAD rate, number of diarrhea days, and length of hospitalization days to the previous monthly and

quarterly rates. The nurse manager of the floor who conducts key performance indicators (KPIs) every end of the month will be responsible for preparing a report utilizing the computer database. Monthly and quarterly AAD rate, CDI rate, diarrhea days, and length of hospitalization days will be compared to the prior rate to see progress/success of this project. Reduction in the monthly AAD rate, CDI rate, diarrhea days, and length of the hospitalization days for typical infections will indicate the succession of this project. However, at this time, this project will not be implemented on the floor as it was planned due to a current pandemic situation and a change in the employment status. So the benchmark project will be utilized for this class's requirement.

If the situation allows, this project will be implemented in a similar population and similar hospital floor in the future. At this time, the PowerPoint presentation of this project will be presented to peers in this class.

## Timetable/Flowchart

From day one of antibiotic initiated, the probiotic will be given along the course of the antibiotic. Any time a physician order an antibiotic in the electronic charting system, the order for probiotic *Culturelle* that consists of LGG will tag along with the order automatically. However, the physician will have a choice to exclude the Culturelle order if there is any contraindication or any other condition that the physician does not want to order probiotic. Once the antibiotic and probiotic are ordered by the physician and verified by the pharmacy, they will be administered by the primary nurse every day along with antibiotics. The nurse will provide education on antibiotics, AAD/CDAD, and probiotics and how to keep a record every day. The nurse will provide a copy of the Bristol stool chart sheet and excel sheet that includes the date, number of stools, and consistency for the patient to keep the record for the next 12 weeks. The nurse will assure the patient understands the importance of accurate reporting of stool

consistency and the number of stools. The nurse will be responsible for charting consistency and times of stools that occurred in every shift in the electronic charting system during hospitalization. The discharge nurse to follow with the patient every week until 12 weeks to keep updated records on the patient's chart. The Nurse Clinician or manager will be responsible for pulling data from Electronic Health Record (EHR) and prepare the AAD rate, CDI rate, days of diarrhea days every end of the month.

## Data Collection Methods

Electronic Health records will be utilized to calculate the AAD rate, CDAD rate, number of diarrhea days, and length of hospitalization days. Discharge follow-up will be made via telephone every week by the nurse clinician until 12 weeks which will be recorded/updated in an electronic health record. These all data will be utilized by the nurse manager to generate aggregate data.

## Cost/Benefit analysis

It is assumed that the cost to the patients due to adding probiotics would be minimum per course per patient when compared to the risk and cost associated with AAD and CDAD. Some of the research studies conducted on the cost-effective analysis of the use of probiotics in preventing AAD and CDAD showed very positive and promising results. A research study conducted by the Provincial Healthcare system in Canada found that the average overall cost per patient who was treated with oral probiotics was Canadian dollar (CAN$) 327 in comparison to CAN$ 845 for the patient who did not receive probiotic therapy during antibiotic therapy (Leal, Heitman, Conly, Henderson, & Manns, 2016). The direct cost of treatment with probiotics was CAN$ 24 per patient per course of treatment (Leal et al., 2016). This study also found that the risk of CDAD was reduced from 5.5% to 2% among the probiotics group (Leal et al., 2016).

Therefore, easily available probiotics will be cost-effective in comparison to the cost burden associated with AAD and CDAD if proven to have protective effects on the elderly population.

## Discussion of the Results

Official evaluation of this benchmark study is not available at this time. The clinical instructor of this class has provided positive feedback on this project. Also, this project has received positive feedback from the peers of this class. This author is very hopeful to utilize this benchmark project in the real work environment to receive actual results in clinical settings.

## Recommendations

AAD and CDAD are the complications associated with antibiotic use that impact the mortality and morbidity among vulnerable populations such as the elderly. Research studies have shown positive effects of using probiotics during antibiotic therapy in preventing or decreasing the symptoms of AAD and CDAD. Easily available and tolerated probiotics can be life-saving as well as cost-effective measures if they help to prevent and improving AAD and CDAD symptoms among the elderly. Consumption of probiotics is very common in our society due to the health benefit they offer. Therefore, it is recommended to prescribe or advise to take probiotics preferably LGG along with antibiotics to reduce the risk of AAD and CDAD among the elderly high-risk population.

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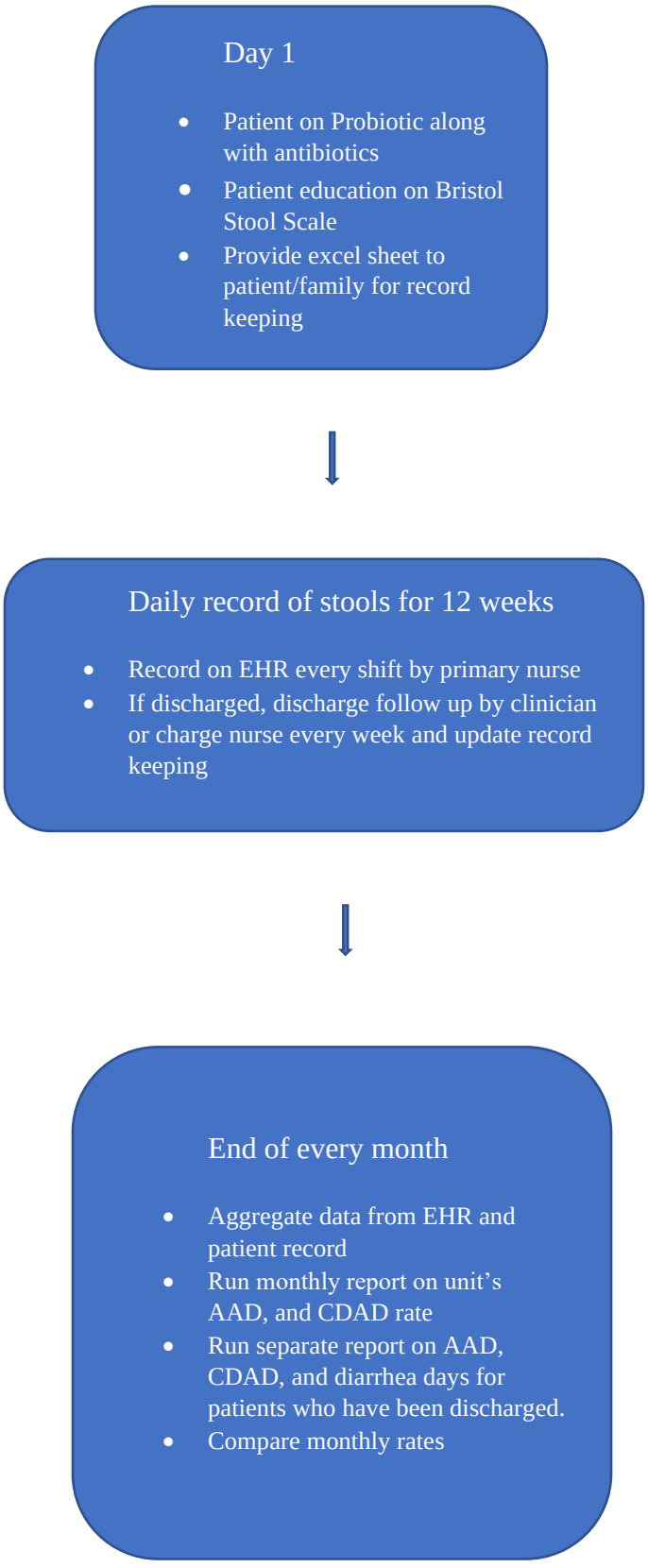
# Appendix A

## Flowchart



Appendix B

Sample: Patient recording sheet

**Patient Name:**

| Date | Number of stool per day | Consistency |
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